Grand Rounds at the Clinical Center of the National Institutes of Health

Evaluating Coronary Heart Disease Risk

Tiles in the Mosaic

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SELECTED CASE

An asymptomatic 34-year-old white man was referred to the Lipid Clinic of the National Heart, Lung, and Blood Institute for atherosclerotic cardiovascular disease risk assessment. His father died at the age of 39 years of a myocardial infarction, and his 2 paternal uncles developed symptomatic coronary artery disease by the age of 40 years. The search for conventional cardiovascular disease risk factors was unrevealing. The patient exercised regularly and had never smoked tobacco products. Physical examination revealed a normotensive man within 5% of his ideal body weight. His fasting concentrations of blood glucose (5.33 mmol/L [96 mg/dL]), low-density lipoprotein cholesterol (LDL-C) (1.76 mmol/L [68 mg/dL]) and high-density lipoprotein cholesterol (HDL-C) (1.06 mmol/L [41 mg/dL]) were all within normal limits. However, his fasting plasma triglyceride concentration was increased (6.64 mmol/L [588 mg/dL]) as was his apolipoprotein B concentration at 3.90 mmol/L (151 mg/dL) (normal range, 1.94-3.33 mmol/L [75-129 mg/dL]). The apolipoprotein A-I concentration was low (2.74 mmol/L [106 mg/dL]; normal range, 2.79-4.42 mmol/L [108-171 mg/dL]), the lipoprotein (a) [Lp(a)] concentration was 0.05 mmol/L (2 mg/dL) (desirable <0.26 mmol/L [<10 mg/dL]), and his plasma homocysteine level was 9 μmol/L (normal range, 4-17 μmol/L). Exercise treadmill and thallium testing did not reveal inducible myocardial ischemia, but the total calcium score of the coronary arteries by electron beam tomography (ultrafast computed tomography) was 147 (normal range, 9-46).

DISCUSSION

Coronary artery disease is endemic in the developed world. This process begins in childhood[1] and leads to heart disease, the most common cause of death in the United States.[2] However, there are some individuals who are at an even greater risk than the general population for developing symptomatic coronary artery disease. The identification of those individuals and the application of techniques to directly interfere with their atherogenic disease process is the central goal of preventive cardiology. Although the "risk factor" concept now permeates medical practice, the present case illustrates that the currently established risk factors do not fully describe a particular individual's propensity for developing symptomatic cardiovascular disease. Therefore, the search for new cardiovascular disease risk factors that would have predictive and therapeutic utility continues.

A family history of premature and aggressive cardiovascular disease is the most remarkable feature in the present case. The development of ischemic heart disease symptoms before the age of 40 years in the men on the paternal side of this patient's family indicates the possibility of a genetic predisposition to atherogenesis. In the absence of the established cardiovascular disease risk factors of obesity, diabetes mellitus, hypertension, and cigarette smoking, other genetic causes for enhanced susceptibility must be considered. The presence of substantial calcification detected by electron beam tomography in this patient's coronary arteries establishes that this patient not only has a positive family history for heart disease, but also a rampant atherogenic process that is independent of the conventionally recognized cardiovascular disease risk factors. What other risk factors can account for disease in this patient? This review will point to new concepts and clinical tools that may be useful to detect and arrest atherogenesis long before it becomes clinically manifest.

History of Cardiovascular Disease Risk Factors

The concept of "risk factors" is a relatively recent one. Early in this century, unique infectious organisms were established to cause specific diseases. The parallel with genetic causes for disease were implicit in the "one gene–one enzyme" of Beadle and Tatum[3] and bolstered the view that defects in specific genes would lead to unique inborn errors of metabolism.[4] With the initiation of the Framingham Heart Study in 1948, the expectation was that causal relationships would be observed among candidate causes for cardiovascular disease. "The cause" of coronary atherosclerosis would be discovered. However, it became apparent through the first decade of the study in Framingham that sole-cause etiologies were not emerging from the study. Instead, a number of different parameters were correlated with the development of cardiovascular disease. The first use of the term "factors of risk" in 1961 was in the context that "no single essential factor has been identified" to cause coronary heart disease.[5] Therefore, these characteristics are like the tiles that are used to make a mosaic. Isolated, the color and consistency of the individual tile does not provide substantial insight, but taken together, a constellation of tiles defines the picture for both the mosaic and for the propensity to develop cardiovascular disease. This clearer definition of risk is useful in the treatment of an individual patient, such as the present case, as well as in applying the principles of public health to reduce cardiovascular disease risk in the general population.

Conventional Cardiovascular Risk Factors

The now-familiar cardiovascular disease risk factors are summarized in Table 1. The term risk factor was not intended to imply causality. The term was established for parameters that would help to identify individuals with increased cardiovascular disease risk. Some of the risk factors including age, sex, and family history cannot be modified. However, these characteristics have been used as a guide to determine the intensity of the therapy directed to those elements which may play a causal role in atherogenesis and that can be modified. The Adult Treat-

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Table 1.—Established Cardiovascular Disease Risk Factors

Nonmodifiable factors
Age
Sex
Family history
Modifiable factors
Cigarette smoking
Obesity
Hypertension
Physical inactivity
Diabetes mellitus
Cholesterol
Elevated low-density lipoprotein cholesterol
Reduced high-density lipoprotein cholesterol

Table 2.—Methods to Detect Atherosclerosis in Men

Technique	Advantages	Disadvantages
Angiography	Established "gold standard," directs interventional therapy	Invasive, expensive, underestimates extent of atherosclerosis
Intravascular ultrasound	Direct visualization of arterial wall, therapeutic implications for angioplasty	Invasive, expensive, not widely available
Transesophageal echocardiography	Detection and quantitation of aortic atherosclerosis, high resolution	Moderately invasive, expensive, not widely available
Carotid ultrasound	Noninvasive, quantitates atheroma, inexpensive	Difficult to standardize
Magnetic resonance imaging	Noninvasive, direct assessment of arterial wall, both structural and flow determination	Not yet linked to clinical decisions, protocols still experimental, expensive
Electron beam tomography	Noninvasive, fast, inexpensive, correlates with cardiovascular events	Only detects calcific atherosclerosis, not yet linked to clinical decisions

ment Panel of the National Heart, Lung, and Blood Institute has used the established risk factors to determine the goals of therapy to lower the concentrations of atherogenic LDLs.[6] In addition to reducing total cholesterol and LDL-C concentrations, the treatment of hypertension and obesity have entered into the mainstream of clinical practice. Moreover, patients are admonished to alter their lifestyles, to discontinue cigarette smoking, and to increase their daily activity to at least 30 minutes on all or on most days of the week. Therefore, the concept of risk factors has evolved from establishing statistical associations to directly modifying factors that modulate the atherogenic process in the arterial wall.

The modification of cardiovascular risk is most clearly established in the reduction of total cholesterol and LDL-C concentrations. The treatment of patients with elevated concentrations of total cholesterol and LDL-C has been shown to reduce the incidence of myocardial infarction,[7-9] cerebrovascular events, cardiovascular death, and all-cause mortality as both "secondary" intervention[10,11] and as "primary" intervention.[12] The treatment of the underlying pathophysiologic process in the artery is the same regardless of whether the patient has or has not already suffered a cardiovascular disease event (secondary or primary intervention). Instead, we are treating the atherosclerosis in patients who have or have not yet experienced a cardiovascular disease event.

The Detection of Cardiovascular Disease

The case that was initially described in this article illustrates that the conventional cardiovascular disease risk factors do not always lead to therapies that can prevent cardiovascular disease. The only conventional risk factor that was present was that of a strongly positive family history. Does this patient have a malignant underlying atherogenic process? The thallium and exercise stress tests did not indicate the presence of flow-obstructing coronary artery disease lesions, but coronary atherosclerosis generally proceeds diffusely[13] and need not result in exercise-induced ischemia. Therefore, as exemplified by this case, conventional cardiovascular risk assessment often does not provide a full picture of a given patient's underlying disease process.

The initial search for risk factors used either the onset of cardiovascular disease symptoms or cardiovascular disease death as the reference correlates. However, human atherosclerosis is an indolent, progressive, and complex process. A classification has recently been devised characterizing 6 types of vascular lesions that have pathophysiologic relevance.[14] New methods are under development to provide a direct assessment of the progression of atherogenesis at the arterial wall prior to the onset of either symptoms or sudden death (Table 2). Angiography has long represented the definitive assessment of coronary artery atherosclerosis; however, detection of flow-limiting lesions may not entirely reflect the risk that a given patient may have for a cardiovascular disease event. In fact, the characteristics of the plaque that subsequently ruptures to produce acute coronary thrombosis cannot be predicted by coronary angiography.[15,16] Therefore, other methods are being used to assess the extent, characteristics, and severity of atherosclerosis that cannot be determined by the "lumenogram" generated by coronary angiography.

Intravascular ultrasound has been developed to evaluate the characteristics of the walls of coronary arteries and has been particularly useful in the setting of angioplasty and the placement of stents.[17] Since the ultrasound probe is at the tip of the catheter used routinely for angiography, it is possible to assess the extent of luminal narrowing as well as detect intracoronary artery mural calcification. In addition, it is now possible to determine the extent of plaque within the coronary artery using intravascular ultrasound.[18] Although this technique is not widely available, it should prove useful in determining the impact of specific interventions on the extent of coronary artery atherosclerosis.

In addition to direct assessment of the coronary arteries, the evaluation of other vascular beds may have clinical utility because of the diffuse nature of atherosclerosis. The risk for cerebral, myocardial, and peripheral vascular disease events has been associated with the severity of aortic atheromatous plaque determined by transesophageal echocardiography.[19] Assessment of carotid artery atherosclerosis by ultrasound correlated with the risk for experiencing a cardiovascular event as well as the efficacy of cholesterol reduction in reducing the risk for a cardiovascular disease event.[10] These findings suggest that non–coronary artery vascular beds may be central to vascular events as well as provide a means of more accurately defining patients prone to cardiovascular morbidity and mortality.

In addition to evaluating the aorta and the carotids, new noninvasive methods are under development to directly investigate the coronary artery wall in vivo. Magnetic resonance imaging of the coronary arteries can give both structural as well as coronary blood flow assessment.[20,21] The information not only correlates with the conventional coronary angiography, but the quantitation and characterization of the arterial plaque itself may become useful in making routine clinical decisions that complement the information derived from coronary arteriography.

Another technique that may prove useful in assessing a patient's cardiovascular disease risk is electron beam tomography (formerly ultrafast computed tomography). This method detects and quantifies the calcification present in the atherosclerotic plaque.[22] Calcification has long been recognized in complex atheromas present in sclerotic vessels, and the first in vivo detection of calcific atherosclerosis by fluoroscopy was reported 70 years ago.[23] The calcification process represents the elaboration of gene products by the differentiated monocyte-macrophage in the arterial wall[24] and the process resembles nascent bone formation.[25] By gating the electron beam to the electrocardiogram, a computed image can be generated in

the moving epicardial coronary arteries. The electron beam tomogram can detect both flow-limiting stenotic lesions as well as calcific atherosclerotic plaque that is present in regions not discernibly abnormal by coronary angiography.[26,27] Recent studies indicate that detection and quantitation of calcific lesions in the coronary arteries is very informative. First, there is a high correlation of calcification with segmental coronary artery atherosclerosis defined histopathologically.[28] Second, for severity of calcification, the area under the receiver operating characteristic curve ranges from 0.712 to 0.857 to predict the extent of luminal area narrowing observed at autopsy. In addition, it compares favorably with the prediction of severity of coronary artery disease by treadmill and thallium stress testing in patients undergoing coronary angiography.[29] Finally, recent data from a prospective study in 1173 asymptomatic subjects indicate that electron beam tomography may be highly effective in predicting cardiovascular disease events.[30] The area under the receiver operating characteristic curve for this predictive power was a remarkable 0.91. The current patient had a coronary artery calcification score of 147. This indicates that this patient's risk for developing a cardiovascular disease event is increased 25 times with a sensitivity and specificity of 0.89 and 0.77, respectively.[30] Therefore, this patient's electron beam tomogram indicates that he has most likely inherited the gene(s) that leads to accelerated calcific atherosclerosis from the paternal side of his family.

New and Proposed Cardiovascular Disease Risk Factors

The search for additional risk factors continues, since nearly 25% of patients with premature cardiovascular disease do not have one of the established risk factors. In addition, the underlying cause of enhanced atherogenesis susceptibility, as exemplified in the current case report, is not established in many individuals with a strong family history of premature symptomatic cardiovascular disease.

Our society is inundated daily in the lay press with a myriad of suggestions for additional risk factors. These range from coffee and garlic consumption to the intake of a variety of macronutrients and micronutrients such as *trans*-fatty acids, folate, and vitamin E. The broad public interest reflects the explosion of novel parameters published in the biomedical research literature which have biologically plausible influences on atherogenesis. As with many multifactorial disease processes, the development of atherosclerosis as well as symptomatic cardiovascular disease is likely to be influenced by a convergence of many different determinants. However, establishing the validity of a proposed risk factor requires careful epidemiologic investigation. It is left to the well-designed clinical trial to finally assess whether the selective modification of a specific risk factor can prevent disease.

The established cardiovascular disease risk factors have all been validated by epidemiologic investigation (Table 1). However, only the treatment of high LDL-C concentrations[6-10] and hypertension[31-33] have been established by clinical trials to reduce cardiovascular morbidity and mortality. Of the more than 100 potential additional cardiovascular disease risk factors that have been proposed, I have selected 17 that are particularly promising and have therapeutic implications (Table 3). The present case is that of a man, however, and it should be noted that a great deal remains to be accomplished in evaluating risk factors and their therapeutic implications in women. All of these risk factors reflect concentrations or activities that are found within blood. The discovery of new risk factors will undoubtedly emerge from the ongoing investigation of cellular gene expression within the arterial wall.

Plasma total cholesterol and LDL-C concentrations do not fully represent the impact that the plasma lipoproteins have on the atherogenic process and the initiation of cardiovascular disease events. Several lipoprotein particle subspecies characterized by their apolipoprotein composition, their size, and their susceptibility to oxidation appear to be proatherogenic (Table 3). Triglyceride-rich apolipoprotein B-100 particles associated with apolipoprotein C-III, apolipoprotein E-2 and E-4 isoforms, and small, dense, cholesterol-poor LDL particles may be particularly atherogenic. The current patient manifests high fasting triglyceride concentrations as well as elevated levels of apolipoprotein B. The increase in the triglyceride-rich apolipoprotein B is observed in type III hyperlipoproteinemia (dysbetalipoproteinemia) and reflects a cholesterol-poor, yet proatherogenic lipoprotein particle. Since a substantial fraction of patients presenting with a myocardial infarction before the age of 60 years have increased plasma concentrations of these particles in the fasting state,[34] it has been suggested that the determination of the concentrations of apolipoprotein B[35] or subspecies of apolipoprotein B particles[36] in hypertriglyceridemic patients may be useful in assessing cardiovascular disease risk.

There are many other proatherogenic factors that can either lead to endothelial dysfunction and death or enhance cellular proliferation within the atheroma. The response to arterial injury elicits a cascade of interrelated processes directed toward healing the injury.[37] Homocysteine[38] and oxidized lipoproteins[39] are toxic to endothelial cells, and there is evidence that some patients may be more likely to have high concentrations of these substances. Alternatively, high concentrations of insulin may stimulate cellular proliferation and be detrimental by increasing the exuberance of the response to the injury.

Table 3.—Proposed Cardiovascular Disease Risk Factors

Proatherogenic
Homocysteine
Lipoprotein particle oxidation
Hyperinsulinemia
Lipoprotein particle subspecies
Apolipoprotein E isoforms
Cholesteryl ester transfer protein
Prothrombogenic
Plasminogen
Fibrinogen
Factor VII
Plasminogen activator inhibitor 1
Lipoprotein (a)
Antiatherogenic
Apolipoprotein A-I
Lecithin-cholesterol acyl transferase
Hepatic lipase
Low-density lipoprotein receptor
Very low-density lipoprotein receptor
Apolipoprotein E

Cardiovascular disease is due to a variety of biological processes including acute thrombosis. There are a number of factors involved in the physiology of clot formation that are risk factor candidates. The initial activation of plasminogen that leads to cleavage of fibrinogen to generate fibrin is a complex process involving an array of plasma proteins and cellular receptors. High concentrations of fibrinogen, which is increased in cigarette smokers, is correlated with the incidence of myocardial infarction. Similarly, plasminogen concentrations, factor VII concentrations, and plasminogen activator inhibitor 1 (PAI-1) levels also correlate with the risk for developing an ischemic event. Since PAI-1 associates with triglyceride-rich lipoproteins, this factor and Lp(a), which contains structural motifs resembling plasminogen, link the plasma lipoproteins with thrombosis. Although the present patient had a low Lp(a) concentration, the sequestration of PAI-1 by his triglyceride-rich lipoprotein may predispose him to thrombosis.

In contrast, antiatherogenic risk factors may attenuate atherosclerotic risk. Candidates for antiatherogenic factors have been generated using transgenic animal models. Subspecies of HDL particles containing apolipoprotein A-I without apolipoprotein A-II, termed LpA-I particles, appear to be especially antiatherogenic. Several enzymes, including hepatic lipase and lecithin:cholesterol acyl transferase (LCAT), modulate HDL metabolism, and LCAT has recently been shown to pre-

vent atherosclerosis in a transgenic animal model.[40] In addition, overexpression of the genes affecting clearance of atherogenic lipoprotein particles, including the LDL receptor, the very low-density lipoprotein receptor, and apolipoprotein E-3, might even be termed "therapeutic" risk factors.[41,42]

In the present case, the presence of substantial calcific coronary artery atherosclerosis defined by electron beam tomography led to the search for other possibilities other than the conventionally accepted cardiovascular disease risk factors. The concentrations of homocysteine and Lp(a) on this patient were normal. The blood concentrations of these 2 substances can be reduced by folate and niacin/LDL apheresis, respectively. Ongoing and future clinical trials are required to determine the efficacy of the reduction of homocysteine and Lp(a) on reducing cardiovascular risk. The "normal" plasma LDL-C concentration was in the context of markedly increased concentrations of triglyceride-rich apolipoprotein B concentrations. Patients with this lipoprotein phenotype experienced a reduced incidence of cardiovascular sequelae with the use of the fibric acid derivative gemfibrozil.[9] Alternatively, niacin, which can reduce the concentrations of these particles as well as raise HDL-C, has been demonstrated to reduce cardiovascular disease sequelae and all-cause mortality in patients with prior myocardial infarction.[8,43] This patient was treated by gradually increasing the niacin dosage to 500 mg of crystalline niacin 3 times a day with meals. This reduced his fasting triglyceride concentrations from 6.64 mmol/L (588 mg/dL) to 3.22 mmol/L (285 mg/dL) and his apolipoprotein B concentrations from 3.90 to 2.78 mmol/L (151 to 107 mg/dL).

In summary, the concept of cardiovascular risk factors is firmly established in routine clinical practice. With the advent of more sensitive and specific screening methods, atherosclerosis detection and risk factor assessment will become more refined. These tools coupled with the results from ongoing clinical trials will permit ever more effective therapy to prevent cardiovascular disease.

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